DESCRIPTION

Meldonium Salts, Method of Their Preparation and Pharmaceutical Compositions on Their Basis.

TECHNICAL FIELD

The present invention relates to 3-(2,2,2-trimethylhydrazinium)propionate salts of the general formula $X^-(CH_3)_3N^+NHCH_2CH_2COOH$ where X^- is an acid anion selected from the group of acid phosphate, acid fumarate, acid oxalate, acid maleate and/or acid pamoate, orotate, galactarate, sulfate, dichloroacetate, acid galactarate, fumarate, taurate, maleate, acid aspartate, creatinate, acid sulfate, magnesium succinate, acid citrate, citrate, succinate, acid succinate, adipinate, acid tartrate and lactate, which distinguish from 3-(2,2,2-trimethylhydrazinium) propionate dihydrate by low hygroscopicity and/or increased thermal stability and/or lasting action. This invention relates also to the method of such salt preparation and to pharmaceutical formulations containing the said salts.

BACKGROUND OF THE INVENTION

3-(2,2,2-Trimethylhydrazinium) propionate is disclosed in US Patent No.4481218.

It is well known that 3-(2,2,2-trimethylhydrazinium) propionate as dihydrate (this substance being known under its International Nonproprietary Name of Meldonium) is widely used for controlling carnitine and gamma-butyrobetaine concentration ratio and consequently the speed of fatty acid beta-oxidation in the body (Dambrova M., Liepinsh E., Kalvinsh I. Mildronate: cardioprotective action through carnitine-lowering effect. Review. // Trends Cardiovasc.Med. – 2002. – Vol. 12, N.6. – P. 275-279. Rupp H., Zarain-Herzberg A., Maisch B. The use of partial fatty acid oxidation inhibitors for metabolic therapy of angina pectoris and heart failure // Herz, 2002. – Vol. 27, N.7. – P. 621-636. Mildronate, Met-88. Drugs Fut. 2001, 26(1), p.82).

Due to these properties, Meldonium (registered with the trade mark of „MILDRONĀTS®" , "MILDRONATE®", "МИЛДРОНАТ®") is extensively applied in medicine as an anti-ischemic un stress-protective drug in treating various cardio-vascular diseases and other pathologies involving tissue ischemia (R.S.Karpov, O.A.Koshelskaya, A.V.Vrublevsky, A.A.Sokolov, A.T.Teplyakov, I.Skarda, V.Dzerve, D.Klintsare, A.Vitols, I.Kalvinsh, L.Matveyeva, D.Urbane. Clinical

efficacy and safety of Mildronate in patients with ischemic heart disease and chronic heart failure. Kardiologiya, 2000 , Vol.6, - P.69-74.)

However, Meldonium as dihydrate has essential drawbacks, the first of which consists in its rather high hygroscopicity. Already after 24 hours maintenance at 100% air humidity, Meldonium mass is increased by 10% because of water absorption, the substance being transformed into a syrup.

Other essential drawback of Meldonium is caused by the half-elimination period equalling 4-10 hours for humans while this drug must be used 2-4 times daily in the clinic (V.Dzērve. Mildronāts. PAS "Grindeks", 1999, p.1), though it is longer in trials on rats (K.Yoshisue, Y.Yamomoto, K.Yoshida, M.Saeki, Y.Minami, Y.Esumi, Y.Kawaguchi. Pharmacokinetics and biological fate of 3-(2,2,2-trimethylhydrazinium)propionate (MET-88), a novel cardioprotective agent, in rats. Drug Metabolism and Disposition, vol.28, No6, 687-694).

As Meldonium dihydrate is unsuitable for single daily oral introduction, it was one of the aims of the present invention to find other pharmacologically acceptable Meldonium forms which would be applicable for single daily use. It is generally known that amino acid betaine salts usually have good solubility in water. If pharmacologically acceptable acids are selected, resorption and elimination pharmacokinetics and biological activity of these salts normally does not much differ from the parameters of the initial compound.

Besides, Meldonium is not very stable: while heated, it fast loses the water of the crystal hydrate. In turn, the anhydrous form of Meldonium is unstable and extremely hygroscopic. In such form, this compound soon becomes coloured and gets a specific annoying odour. Thus, the hygroscopicity and thermal non-stability of Meldonium dihydrate are significant disadvantages restricting the possibilities of preparing different oral and external drug dosage forms from this compound. Furthermore, Meldonium dihydrate is actively dehydrated at temperatures so low as 40-45°C. This means that sure storage of Meldonium dosage forms containing crystal hydrate is rather embarrassing in countries with hot climate.

Because Meldonium dihydrate is not readily applicable for producing drug oral dosage forms, it was a further object of this invention to find other pharmacologically acceptable salts of Meldonium which would lack hygroscopicity or/and, be thermally stable and could be stored in any climatic zone for a long time.

DETAILED DESCRIPTION OF THE INVENTION

For most Meldonium salts, their pharmacokinetic properties practically do not differ from those described for Meldonium. Therefore the use of these salts for preparing pharmaceutical compositions seemingly have no advantage as compared to Meldonium.

To our surprise, we suddenly found that Meldonium salts of some pharmaceutically acceptable polybasic acids are an exception in this respect; although readily soluble in water, they essentially differ from Meldonium by their pharmacokinetic and pharmacodynamic properties.

It was an astonishing discovery since no theoretical argument exists why Meldonium salts, which are easily soluble in water should have resorption and elimination speed different from that of Meldonium.

Nevertheless, we succeeded in finding among the above salts some specific Meldonium salts with appropriate pharmacokinetics and pharmacodynamics allowing their single daily use; they are: $X^-(CH_3)_3N^+NHCH_2CH_2COOH$ where X^- is the anion of acids is selected from the group of mono-substituted fumaric acid, mono-substituted phosphoric acid, mono-substituted oxalic acid, mono-substituted maleic acid un mono- and/or di-substituted galactaric, pamoic acids and orotic acid.

It is common knowledge that betaines of amino acids are commonly relatively stable substances. It is well known that these compounds are readily soluble in water and the biological activity of their pharmacologically acceptable salts usually does not differ from that of the initial compound.

However, Meldonium and monobasic, dibasic as well as tribasic pharmaceutically acceptable acid salts have equal or even higher hygroscopicity than Meldonium itself. Moreover, many of them cannot be prepared in crystalline form at all because they form syrups containing variable quantity of water.

The salts of both strong and weak acids, viz. Meldonium sulfate, hydrogen chloride, acetate, lactate, citrate as well as salts of many other pharmaceutically acceptable acids are hygroscopic. Consequently, using these salts for preparation of pharmaceutical compositions for oral use is deemed lacking preference to that of Meldonium .

We noticed completely unexpectedly that Meldonium salts of some pharmaceutically acceptable polybasic acids are exceptional in this regard; they

proved to be practically non-hygroscopic though easily soluble in water. We observed that these compounds are also very stable while maintained at both room temperature and temperatures up to at least 50 centigrade over a long period of time. Similarly we gained the unanticipitated result that such specific monobasic acid as orotic acid forms a non-hygroscopic Meldonium salt, too. All of the claimed salts proved more stable thermally than Meldonium .

Orally administered Meldonium is easily bioavailable also from these salts, therefore these salts are much more suitable for preparing various drug dosage forms than the hygroscopic and thermally unstable Meldonium. It was an astounding discovery because no theoretical underpinning suggests any difference of Meldonium orotate or polybasic acid salts, which are also readily soluble in water, from other salts as to hygroscopicity.

Since they are not hygroscopic and/or have increased thermal stability, these salts can be easily handled and are favourably suitable for manufacturing solid administration forms. Their aqueous solutions are less acid than those of the corresponding chlorides: consequently these salts are also more suitable for manufacturing injectable administration forms.

The following non-limiting examples illustrate the preparation of salts according to the present invention.

EXAMPLE 1

The following methods may be applied for the preparation of these salts. Meldonium is dissolved in water or other appropriate solvent, an equimolar quantity of a polybasic acid selected from the group of fumaric acid, phosphoric acid, aspartic acid, citric acid, lactic acid, maleic acid, oxalic acid, or orotic acid (the latter is taken in semi-molar quantity) is added, and the mixture is stirred at temperature from 20 to 50°C till the corresponding salt is formed. At the second technological stage, Meldonium salts are evaporated to dryness if necessary. At the third technological stage, in case of need the obtained salts are recrystallised from a suitable solvent.

EXAMPLE 2

The said salts can also be prepared from the corresponding salts of Meldonium production intermediates, viz. methyl- or ethyl-esters of 3(2,2,2,-trimethylhydrazinium) propionate, the latter being heated together with the corresponding acids in aqueous or aqueous-alcoholic solutions, and subsequent

treatment, eduction and purification being performed by analogy with the first method of preparation.

EXAMPLE 3

Method of salt preparation from meldonium dihydrate. Meldonium and the corresponding acid are dissolved in a small quantity of water at 40-50°C under stirring. The obtained solution is evaporated in vacuum at 40-50°C. Acetone or acetonitrile is added to the formed mass (what predominantly is viscous syrup), and the mixture is grated. The precipitated crystalline mass is stirred in acetone or acetonitrile during several hours, filtered off, washed with acetone or acetonitrile, dried in vacuum at room temperature.

Sample hygroscopicity was tested by H_2O content determination before the test and after 24 hours maintenance at 100% humidity (keeping in a closed vessel over water). On such conditions, Meldonium absorbs 10% water (as to mass increase) during 24 hours. Water content was determined by titration by Fischer's method; in cases of syrup formation water content is determined by sample mass increase.

The claimed invention is illustrated by, but not restricted to the following examples of salts obtained by the above method:

EXAMPLE 4

Meldonium orotate (1:1). Mp. 211-214°C. ^{1}H NMR spectrum (D_2O), δ, ppm: 2.56 (2H, t, CH_2COO^-); 3.29 (2H, t, CH_2N); 3.35 (9H, s, Me_3N^+); 6.18 (1H, s, –CH=). Found, %: C 43.78; H 6.01; N 18.48. Calculated, %: C 43.71; H 6.00; N 18.53. Initially H_2O content in the sample was 0.3919%; during 24 hours at 100% humidity it remains unchanged.

EXAMPLE 5

Meldonium phosphate (1:1). Mp.158-160°C. ^{1}H NMR spectrum (D_2O), δ, ppm: 2.60 (2H, t, CH_2COO^-); 3.31 (2H, t, CH_2N); 3.35 (9H, s, Me_3N^+). Found, %: C 29.64; H 7.05; N 11.33 Calculated, %: C 29.51; H 7.02; N 11.47. Initially H_2O content in the sample was 0.0762%; during 24 hours at 100% humidity it remains unchanged.

EXAMPLE 6

Meldonium fumarate (1:1). Mp. 140-142°C. ^{1}H NMR spectrum, δ, ppm: 2.57 (2H, t, CH_2); 3.29 (2H, t, CH_2); 3.35 (9H, s, Me_3N^+); 6.72 (2H, s, –CH=CH–). Found, %: C 45,46; H 6,94; N 10,72. Calculated, %: C 45,80; H 6,92; N 10,68. Initially H_2O

content in the sample was 0.18%; during 24 hours at 100% humidity it remains unchanged.

EXAMPLE 7

Meldonium oxalate (1:1). Mp. 123-125°C . ^{1}H NMR spectrum (D_2O), δ, ppm: 2.61 (2H, t, CH_2COO^-); 3.30 (2H, t, CH_2N); 3.35 (9H, s, Me_3N^+). Found, %: C 40.86; H 6.82; N 11.78 Calculated, %: C 40.68; H 6.83; N 11.86. Initially H_2O content in the sample was 0.1661%; after 24 hours maintenance at 100% humidity it was 3.1211%.

EXAMPLE 8

Meldoniuma maleate (1:1). Mp. 98-100°C. ^{1}H NMR spectrum (D_2O), δ, ppm: 2.60 (2H, t, CH_2COO^-); 3.31 (2H, t, NCH_2); 3.35 (9H, s, Me_3N^+); 6.35 (2H, s, –CH=CH–). Found, %: C 45.93; H 6.95; N 10.65. Computational, %: C 45.80; H 6.92; N 10.68. Initially H_2O content in the sample was 0.387%; after 24 hours maintenance at 100% humidity it was 4.6844%.

EXAMPLE 9

Meldonium mucate (galactarate; 2:1; ×H_2O). Mp.152-154°C. ^{1}H NMR spectrum (D_2O), δ, ppm: 2.46 (4H, t, 2 × CH_2COO^-); 3.26 (4H, t, 2 × NCH_2); 3.35 (18H, s, 2 × Me_3N^+); 3.98 un 4.31 – two singlets of low intensity, protons of mucic acid. Found, %: C 42.13; H 7.58; N 10.77. Calculated, %: C 41.53; H 7.75; N 10.76. Initially H_2O content in the sample was 3.0414%; after 24 hours maintenance at 100% humidity it was 7.6830%.

EXAMPLE 10

Meldonium pamoate (1:1; x H_2O). Meldonium (5.46 g, 30 mmol) and pamoic acid (5.82 g, 15 mmol) are mixed with water and acetone (15 + 15 ml), the formed suspension is evaporated, 30-40 ml toluene is added to the residual viscous mass, it is grated, and evaporation is repeated. If the residue is insufficiently dry, treatment with toluene is repeated. Mp. 128-133°C (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.41 (2H, t, CH_2COO^-); 3.14 (2H, t, CH_2N); 3.25 (9H, s, Me_3N^+); 4.75 (2H, s, $–CH_{2–(pam.)}$); 7.12 (2H, t, H_{arom}); 7.26 (2H, td, H_{arom}); 7.77 (2H, d, H_{arom}); 8.18 (2H, d, H_{arom}); 8.35 (2H, s, H_{arom}). Found, %: C 62,90; H 5,83; N 4,98. Calculated, %: C 63,07; H 5,84; N 5,07. Initially H_2O content in the sample was 1.71%; after 24 hours maintenance at 100% humidity sample mass increased by 9% due to absorbed water.

EXAMPLE 11

Meldonium sulfate (2:1). T_m 80-182°C (decomp.). ^{1}H NMR spectrum (D_2O), δ, ppm: 2.60 (4H, t, 2 × CH_2COO^-); 3.30 (4H, t, 2 × CH_2N); 3.35 (18H, s, 2 × Me_3N^+). Found, %: C 37.08; H 7.73; N 14.29; S 8.20. Calculated, % : C 36.91; H 7.74; N 14.35; S 8.21. Initially H_2O content in the sample was 0.313%; after 24 hours maintenance at 100% humidity sample mass increased by 11.8% due to absorbed water.

EXAMPLE 12

Meldonium dichloroacetate (1:1). Mp. 86-88°C. ^{1}H NMR spectrum (D_2O), δ, ppm: 2.61 (2H, t, CH_2COO^-); 3.31 (2H, t, CH_2N); 3.35 (9H, s, Me_3N^+); 6.05 (1H, s, – $CHCl_2$). Found, %: C 35.13; H 5.85; N 10.10. Calculated, %: C 34.92; H 5.86; N 10.18. Initially H_2O content in the sample was 1.17%; after 24 hours maintenance at 100% humidity sample mass increased by 12% due to absorbed water.

EXAMPLE 13

Meldonium mucate (galactarate; 1:1). Mp. 152-154°C. ^{1}H NMR spectrum (D_2O), δ, ppm: 2.47 (2H, t, CH_2COO^-); 3.26 (2H, t, CH_2N); 3.35 (9H, s, Me_3N^+); 3.71 and 3.98 – two singlets of low intensity, protons of the slightly soluble mucic acid. Found, %: C 40.22; H 6.75; N 7,75%. Calculated, %: C 40,22; H 6,79; N 7,86. Initially H_2O content in the sample was 1.98%; after 24 hours maintenance at 100% humidity it was 12.8 % .

EXAMPLE 14

Meldonium fumarate (2:1). Mp. 156-158°C. ^{1}H NMR spectrum (D_2O), δ, ppm: 2.53 (4H, t, 2 × $CH_{2(meld)}$); 3.29 (4H, t, 2 × $CH_{2(meld)}$); 3.35 (18H, s, 2 × Me_3N^+); 6.65 (2H, s, –CH=CH–$_{(fum.ac.)}$). Found, %: C 46.68; H 7.91; N 13.69. Calculated, %: C 47.05; H 7.90; N 13.72. Initially H_2O content in the sample was 1.5136%; after 24 hours maintenance at 100% humidity it was 13.4707%.

EXAMPLE 15

Meldonium 2-aminoethane sulfonate (taurate; 1:1; ×1.5H_2O). Mp. 190-193°C (with decomp.). ^{1}H NMR spectrum (D_2O), δ, ppm: 2.38 (2H, t, CH_2COO^-); 3.18-3.30 (4H, m, $NCH_{2(meld.)}$ + $CH_{2(taur.)}$); 3.34 (9H, s, Me_3N^+); 3.42 (2H, t, $CH_{2(taur.)}$). Found, %: C 32.40; H 8.16; N 13.98; S 10.60. Calculated, %: C 32.21; H 8.11; N 14.08; S 10.75. Initially H_2O content in the sample was 9,4824%; after 24 hours maintenance at 100% humidity it was 17.0854%.

EXAMPLE 16

Meldonium maleate (2:1). Mp. 104-106°C. ^{1}H NMR spectrum (D_2O), δ, ppm: 2.54 (4H, t, CH_2COO^-); 3.30 (4H, t, CH_2N); 3.35 (18H, s, Me_3N^+); 6.42 (2H, s, –CH=CH–). Found, %: C 46.59; H 7.88; N 13.50. Calculated: C 47.05; H 7.90; N 13.72. Initially H_2O content in the sample was 1.3595%; after 24 hours maintenance at 100% humidity sample mass increased by 18% due to absorbed water.

EXAMPLE 17

Meldonium L-(+)-aspartate (1:1; ×2H_2O). Mp. 146-148°C. ^{1}H NMR spectrum (D_2O), δ, ppm: 2.49 (2H, t, CH_2COO^-); 2.70-2.99 (2H, m, $CH_{2(asp.)}$) 3.27 (2H, t, CH_2N); 3.35 (9H, s, Me_3N^+); 3.95 (1H, dd, $CHNH_2$). Found, %: C 37.71; H 7.85; N 13.03. Calculated, %: C 38.09; H 7.99; N 13.33. Initially H_2O content in the sample was 12.5%; after 24 hours maintenance at 100% humidity sample mass increased by 18% due to absorbed water.

EXAMPLE 18

Meldonium creatinate (1:1; ×3H_2O). Mp. 227-228°C (decomp.). ^{1}H NMR spectrum (D_2O), δ, ppm: 2.38 (2H, t, CH_2COO^-); 3.03 (3H, s, $NMe_{(creatine)}$); 3.22 (2H, t, CH_2N); 3.35 (9H, s, Me_3N^+); 3.92 (2H, s, $NCH_{2(creatine)}$). Initially H_2O content in the sample was 15.8%; after 24 hours maintenance at 100% humidity sample mass increased by 18% due to absorbed water.

EXAMPLE 19

Meldonium sulfate (1:1). T_m 98-100°C. ^{1}H NMR spectrum (D_2O), δ, ppm: 2.62 (2H, t, CH_2COO^-); 3.31 (2H, t, CH_2N); 3.35 (9H, s, Me_3N^+). Found, % C: C 29.23; H 6.57; N 11.17; S 13.10. Calculated: C 29.50; H 6.60; N 11.47; S 13.13. Initially H_2O content in the sample was 1.4189%; after 24 hours maintenance at 100% humidity sample mass increased by 20% due to absorbed water.

EXAMPLE 20

Meldonium magnesium succinate (1:1:1; ×2H_2O). (see Meldonium-magnesium tartrate). Mp. 135-140°C (decomp.). ^{1}H NMR spectrum (D_2O), δ, ppm: 2.39 (2H, t, CH_2COO^-); 2.46 (4H, s, $–CH_2–CH_{2–(succin.ac.)}$); 3.22 (2H, t, CH_2N); 3.35 (9H, s, Me_3N^+). Found, %: C 36.66; H 7.28; N 8.37. Calculated: C 37.23; H 6.87; N 8.68. Initially H_2O content in the sample was 10.1215%; after 24 hours maintenance at 100% humidity sample mass increased by 20% due to absorbed water.

EXAMPLE 21

Meldonium magnesium citrate (1:1:1; ×2H_2O) (see Meldonium-magnesium tartrate). Mp. 195-200°C (decomp.). ^{1}H NMR spectrum (D_2O), δ, ppm: 2.48 (2H, t, CH_2COO^-); 2.75 (4H, dd, 2×$CH_{2(citr.)}$); 3.26 (2H, t, CH_2N); 3.34 (9H, s, Me_3N^+). Found, %: C 36.58; H 6.09; N 6.96. Calculated: C 36.34; H 6.10; N 7.06. Initially H_2O content in the sample was 9.45%; after 24 hours maintenance at 100% humidity the sample diffused.

EXAMPLE 22

Meldonium citrate (1:1). Mp. 90-95°C (decomp.).^{1}H NMR spectrum (D_2O), δ, ppm: 2.56 (2H, t, CH_2COO^-); 2.85 (4H, dd, 2×$CH_{2(citr.)}$); 3.28 (2H, t, CH_2N); 3.35 (9H, s, Me_3N^+).

EXAMPLE 23

Meldonium citrate (2:1). Mp. 101-107°C (decomp.).^{1}H NMR spectrum (D_2O), δ, ppm: 2.51 (4H, t, 2×CH_2COO^-); 2.81 (4H, dd, 2×$CH_{2(citr.)}$); 3.26 (4H, t, 2×CH_2N); 3.35 (18H, s, 2× Me_3N^+).

EXAMPLE 24

Meldonium succinate (1:1). Mp. 95-100°C (decomp.).^{1}H NMR spectrum (D_2O), δ, ppm: 2.51 (2H, t, $CH_{2(meldon.)}$); 2.60 (4H, s, –CH_2–CH_2–$_{(succin.ac.)}$); 3.27 (2H, t, $CH_{2(meldon.)}$); 3.35 (9H, s, Me_3N^+).

EXAMPLE 25

Meldonium succinate (2:1). Mp. 103-107°C (decomp.).^{1}H NMR spectrum (D_2O), δ, ppm: 2.47 (4H, t, 2 × $CH_{2(meldon.)}$); 2.59 (4H, s, –CH_2–CH_2–$_{(succin.ac.)}$); 3.29 (4H, t, 2 × $CH_{2(meldon.)}$); 3.35 (18H, s, 2 × Me_3N^+).).

EXAMPLE 26

Meldonium adipinate (2:1). Mp. 110-114°C (decomp.).^{1}H NMR spectrum (D_2O), δ, ppm: 1.55-1.70 (4H, m, 2×$CH_{2(adip.)}$); 2.28-2.39 (4H, m, 2×$CH_{2(adip.)}$); 2.45 (4H, t, 2×$CH_{2(meldon.)}$); 3.24 (4H, t, 2×$CH_{2(meldon.)}$); 3.34 (18H, s, 2 × Me_3N^+).

EXAMPLE 27

Meldonium tartrate (1:1). Mp. 100-107°C (decomp.). ^{1}H NMR spectrum (D_2O), δ, ppm: 2.57 (2H, t, CH_2COO^-); 3.29 (2H, t, $CH_{2(meldon.)}$); 3.35 (9H, s, Me_3N^+); 4.55 (2H, s, $CH_{(tart.ac.)}$).

EXAMPLE 28

Meldonium lactate (1:1). Mp. 110-114°C (decomp.).^{1}H NMR spectrum (D_2O), δ, ppm: 1.33-1.48 (3H, m, $Me_{(lact.ac.)}$); 2.50 (2H, t, CH_2COO^-); 3.26 (2H, t, $CH_{2(mildr.)}$); 3.35 (9H, s, Me_3N^+); 4.21 (1H, q, $CH_{(lact.ac.)}$).

This invention relates also to pharmaceutical formulations containing at least one of the Meldonium salts described herein as pharmaceutical active and pharmaceutically acceptable solid or liquid excipients used in drug dosage form production. Solid formulations suitable for producing dosage forms of oral introduction as well as syrups and solutions containing the claimed salts and excipients are preferable.

In case when the active substance(s) is (are) inserted into tablets, caplets, pills, granules, powders, or capsules, they shall contain a Meldonium salt from 0,5 to 5 gr. per tablet, caplet, pill, capsule or one portion of powder or granules.

The following non-limiting examples illustrate the pharmaceutical formulation of salts for solid formulation

EXAMPLE 29 Formulation for manufacturing tablets:

A Meldonium salt according to the invention	500 mg
Starch	20 mg
Talc	10 mg
Ca-stearate	1 mg
Total	531 mg

The following non-limiting examples illustrate composition suitable for producing capsules is the following :

EXAMPLE 30

A Meldonium salt according to the invention	500 mg
Starch	66mg
Talc	26 mg
Ca-stearate	3 mg
Total	602 mg

In case if the active(s) are introduced by injections or orally by means of drops, a syrup or beverage, the pharmaceutical formulation shall contain a Meldonium salt according to this invention in a ratio of 0,5 to 60% by weight and a pharmaceutically admissible solvent, e.g. distilled water, an isotonic, glucose or buffer solution or mixtures of them.

The following non-limiting examples illustrate the pharmaceutical formulation of salts for injectable administration or/and orally administration:

EXAMPLE 31

Injection formulation:

A Meldonium salt according to the invention	500 mg
Water for injections	5ml

EXAMPLE 32

A syrup formulation:

A Meldonium salt according to the invention	25.00 mg
Methyl-p-hydroxybenzoate	0.20-0.60 g
Propyl-p-hydroxybenzoate	0.01-0.1 g
Propylene glycol	6.15-8.30g
Sorbit	120.00-150.50 g
Glycerine	10.00-15.00 g
Purified water	108ml
Total	250ml

In case of trans-dermal application of the active(s), it's (their) content in an cream, gel, solution, ointment or plaster shall be 0.5-40% by weight.

The following non-limiting examples illustrate the pharmaceutical formulation of salts for trans-dermal (local/topical) administration:

EXAMPLE 33

Gel formulation:

A Meldonium salt according to the invention	10,00%

Sodium starch glycollate type C,	4,00
Propylene glycol	2,00
Fumaric acid	0,40
Purified vater	83,40

In the case the salt are administered rectally their content in a suppository or microenema accounts for 0.5 to 40 % by weight.